UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/295,925	04/21/1999	PHALGUN B. JOSHI	16303-007510	7753

20350 7590 11/19/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/295,925	JOSHI ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 18, 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-10,12 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,12 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application filed April 21, 1999 claims benefit to provisional applications: 60/028,665, filed April 22, 1998; 60/111,653, filed December 9, 1998; and 60/111,637, filed December 9, 1998.

Applicants' amendment filed August 22, 2003 has been received and entered. Claims 6, 11, 13-45 have been canceled. Claims 1-5 and 12 have been amended. Claims 1-5, 7-10, 12 and 46 are pending and currently under examination

Specification

The specification objected to as failing to provide proper antecedent basis for the claimed subject matter of "high energy" is withdrawn.

The amendment to the claims to delete this term has obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 11 and 12 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

The amendment to the claims to delete the recitation of "high energy radiation" has obviated the basis of the rejection.

Claims 1-5, 7-10, 12 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the limitation that "said efficiency of transfection is increased at least about fivefold over cells not contacted with said electromagnetic radiation" is considered new matter. Initially, it is noted that the portions of the specification pointed to and relied upon by Applicants is in a working example. Upon review of the specification Examiner agrees that this portion of the specification provides literal support for the limitation, however this limitation is simply a summary of the results for the working example. Importantly, this particular limitation represents a result of using specific vectors, conditions and method steps and would not simply extend to other conditions. For example, in another working example, particular conditions encompassed by the claims only resulted in a 3 fold increase (see page 53, lines 24-25 and as set forth in figure 15). Clearly, these specific limitations represent summaries

of specific conditions that do not and would not necessarily extend to other specific conditions used in practicing the claimed method. In this case, it is found that the specific fold increase in efficiency recited in claim 1 is not specifically associated even in passing with the generic concept Applicants consider the inventive concept of the invention. The situation is analogous to that decided by the courts in *Purdue Pharma L.P. v. Faulding Inc.* (56 USPQ 2D 1481 99-1416-1433, CAFC 2000) where specific characteristics from examples were found not to be supported in the general disclosure of the genus claimed. In the instant case, there is nothing in the specification that teaches even in passing that an increase in efficiencies of 'at least about fivefold' was specifically contemplated, or that it pertains specifically to the generic aspect of practicing the method in the full breadth as claimed.

It is noted that the specification does provide literal support for other specific increases in efficiencies generically contemplated (bridging pages 11-12), however these are not recited nor encompassed by the instant claim. It should be noted that upon review of the specification and the art of record, in particular the working examples as set forth above, that each of the limitations contemplated may not fully enabled. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the

invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Further, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel.* In this case, the specification fails to provide the necessary guidance to practice the invention as claimed. For example, the specification contemplates a greater than tenfold increase in the number of cells transformed as compared to control cells (top of page 12), however the two working examples discussed above clearly demonstrate that using the specific two conditions for delivery encompassed by the claims do not meet this limitation for increase in efficiency. Further, given the teachings of the art of record differences in transformation efficiencies would be expected to be different depending on the time the transfection step was done. For example, Yorifuji *et al.* (FEBS Letter, 1989) teaches that transformation efficiency changes throughout the cell cycle (see results in figure 1 and the description on page 202, last paragraph in the first column). While certain types of optimization for methodology may be expected, Yorifuji *et al.* clearly set forth circumstances raising issue with dependent claims

encompassing specific points during the cell cycle. Moreover, the examples provided by Yorifuji *et al.* represent truly optimized circumstances of cells in culture wherein most of the cells are synchronized (page 202, section 3). As discussed during the prosecution of the instant specification, the use of radiation *in vitro* and *in vivo* does not result in such a high and pure population of synchronized cells. As set forth in the previous office action, it is recognized in the art that electromagnetic radiation that alter the DNA of a cell, such as x-ray and γ-ray radiation, can cause the cell to stop cycling at specific cell cycle check point until the damaged DNA is repaired. However, a limitation to this is providing a dose radiation which will not kill the cell instead of synchronizing. Spang-Thomsen *et al.* teach that irradiation causes a change in the proliferation kinetics of cells (see summary in abstract). More specifically, Spang-Thomsen *et al.* teach that the treatment results in the synchronization of a small portion of cells, and that it is generally in a dose dependent manner (page 849, second column). However, the maximum percentage of synchronized cells obtained by Spang-Thomsen *et al.* is only 20% (page 851, middle of first column and figure 1). Importantly, Spang-Thomsen *et al.* teach that larger doses of radiation "result in a large fraction of radiation-induced necrotic cells" (page 851, bottom of first column). Therefore, even with increasing doses of radiation, the art teaches that a maximum number of cells which can be synchronized is 20% before the increasing radiation results in killing a large fraction of the cells. Spang-Thomsen *et al.* teach that the maximum number of cells which are synchronized by x-rays is 20% and that increasing doses of radiation result in increasing necrotic cell death. Again the specification relies on the art for the administration of

radiation to practice the claimed method, and provides no specific guidance to overcome any limitation which may present in the art. Given the evidence of Spang-Thomsen *et al.* that increasing amounts of radiation do not simply result in increasing number of synchronized cells, rather these conventional methods known in the art result in increasing cell death, and absence of any specific teaching in the instant specification for providing a solution to this art recognized problem, the specification fails to provide the required teaching and necessary guidance to overcome art recognized problems to practice the methods as instantly claimed. Consequently, based on the working examples and the art of record as discussed above the specification fails to address important issues regarding the necessary teaching to specific conditions to achieve a particular number of synchronized cells with radiation and issues regarding providing specific efficiencies of transformation required to practice the method as claimed.

In summary, the specification fails to provide any description of the specific conditions that would result in the efficiencies required by the instant claims. The dependent claims are included in the basis of the rejection because they fail to describe any particular element of the nucleic acid being delivered that would result in the expression levels recited, and as discussed above it does not appear that from the working examples nor from the specification in general that the particular expression levels required after practicing the method steps were specifically contemplated generically or for any of specific limitations set forth in the dependent claims. Therefore, in view of the lack of guidance, working examples, breadth of the claims, the level of

skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-5, 7-10, 12 and 46 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendment to the claims to delete the recitation of "high energy radiation" has obviated the basis of the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-9, 12 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* and Spang-Thomsen *et al.*

It is noted that the instant claims have been amended to delete specific percentages of cells being synchronized and amended to encompass a 'fivefold increase in efficiency' in transfection. Yorifuji *et al.* specifically teach that using synchronized cells " provides maximal transformation [that] was 7-8 times higher" than that of control cells (page 202, section 3). More specifically, Yorifuji *et al.* teach that the cell cycle phase of cells affects the ability of the cell to be transformed with exogenous DNA, in particular that synchronized cells demonstrate a higher transformation efficiency when they are in S and G2/M phase of the cell cycle (page 202-203; figures 1 and 2). Further, Yorifuji *et al.* use the thymidine kinase gene, a foreign to the transformed cells, which is toxic to said cells when cultured in the appropriate conditions. Yorifuji *et al.* conclude that G2/M phase is the most efficient period for transformation (page 203; bridging paragraph of column 1 and 2). Yorifuji *et al.* teach that different methods of synchronization result gave similar results indicating that the effect is due to synchronization, however does not teach use of electromagnetic radiation to synchronize the cells. Spang-Thomsen *et al.* teach that cells can be synchronized with different amounts of x-ray radiation (page 852; figure 2 and summarized in discussion). Further, Spang-Thomsen *et al.* teach that cellular sensitivity is dependent on the position of the cell in the cell cycle (page 849, citing references 1 and 2) and that optimization of the radiation dose can be used to synchronize a cell population. Therefore, it would have been *prima facie* obvious to one having ordinary skill in

the art at the time the invention was made to synchronize the cells as taught by Spang-Thomsen *et al.* in order to increase the efficiency of stable gene transfer as observed by Yorifuji *et al.* One having ordinary skill in the art would have been motivated to use electromagnetic radiation in order to avoid the need or complicating effects of chemicals to simplify the method of synchronization. There would have been a reasonable expectation of success given the results that different methods of synchronization were effective in increasing the transformation efficiency and thus cell cycle dependent (page 203; second column) suggesting that any form of synchronization would be effective including the x-ray radiation taught by Spang-Thomsen *et al.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 10 rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* in view of Spang-Thomsen *et al.* as applied to claims 1-9, 12 and 46 above, and in further view of Son *et al.*

As discussed above, Yorifuji *et al.* in view of Spang-Thomsen *et al.* teach a method to synchronize cells with electromagnetic radiation to increase the efficiency of transformation with exogenous DNA, however they do not teach to specifically transform the cell with a lipid-nucleic acid particle. At the time of filing the use of liposomes to deliver a nucleic acid to a cell were well known and routinely used in the art. Son *et al.* teach a method to transform a cell with lipid-nucleic acid particle (page 12669; bottom of second column). In particular, Son *et al.* teach that

the use of a DNA liposome composition increases the efficiency of transformation efficiency as compared to the delivery of DNA alone (see results for affect of liposome formulation in figure 2) and can be used in conjunction with other agents to increase the efficiency even more (see results of using CP in figure 3). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to transform the synchronized cells as taught by Yorifuji *et al.* and Spang-Thomsen *et al.* with the method taught in Son *et al.* One having ordinary skill in the art would have been motivated to use lipid-nucleic acid particles to simplify the method of transfection and to make it applicable to cells which may be sensitive to transformation by electroporation. There would have been a reasonable expectation of success given the results of Son *et al.* that the method of transformation which uses the lipid-nucleic acid particle could be used for synchronized cell cultures.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Reynolds

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600